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PYRROLE CHEMISTRY XXV: A SIMPLIFIED SYNTHESIS OF SOME 3-SUBSTITUTED PYRROLES

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Abstract: A new synthesis is reported which allows the rapid preparation in good yield of 3-aroyl-, 3-acetyl- and 3-nitro- pyrroles from pyrrole utilizing the 1-benzenesulfonyl group as a blocking group.

In our first paper on pyrrole chemistry[2] we noted that N-methylated pyrroles gave more β-substitution in electrophilic attack than did the N-unsubstituted ones. Later we showed that the N-benzyl group greatly increased β-substitution.[3] When added to the observations of others, the conclusion seemed to be that steric effects were very important in determining α/β ratios. Thinking that attachment of the pyrrole nitrogen to a polymer might greatly enhance β-attack by electrophiles we chose to examine the Friedel-Crafts acylation of 1-benzenesulfonylpyrrole[4] as a model before attachment of pyrrole to a sulfonated resin such as one of the Amberlyst type.

The Friedel-Crafts benzoylation of 1-benzenesulfonylpyrrole in refluxing dichloromethane with benzoyl chloride/aluminum chloride gave entirely 3-benzoyl-1-benzenesulfonylpyrrole. The benzenesulfonyl group was easily removed from the pyrrole nitrogen by refluxing the crude product with Triton B in aqueous tetrahydrofuran giving 3-benzoylpyrrole (60% yield from pyrrole). This procedure provides a convenient path to 3-benzoylpyrrole in addition to those already available.[5] One of us is interested in 3-aroylpyrroles for further studies, so we have used this method to prepare 3-(4-methylbenzoyl)-pyrrole, 3-(2-methylbenzoyl)-pyrrole and 3-(4-methoxybenzoyl)-pyrrole.[6] Yields have not yet been optimised, but are quite satisfactory for rapid preparative purposes. Nitration of 1-benzenesulfonylpyrrole also gave the 3-substituted product providing a particularly useful route, through hydrolysis, to 3-nitropyrrole free from contamination with the isomer, 2-nitropyrrole, that made the purification difficult in earlier syntheses.[7]

The Friedel-Crafts acetylation and the ethyl glyoxalylation of 1-benzenesulfonylpyrrole were less selective and gave mixtures of 2- and 3- substituted products. Friedel-Crafts or Vilsmeier formylation (with dichloromethyl butyl ether/$AlCl_3$ or dimethylformamide/phosphorus oxychloride respectively) and cyanation with chlorosulphonyl isocyanate or cyanogen bromide/$AlCl_3$ gave almost exclusively the 2-substituted products. In the Friedel-Crafts reactions the best overall yields were obtained using ~2 mole of $AlCl_3$ to 1 mole of the pyrrole and we noted that the ratio of 2-:3- acetylation in the isolated product was dependent on the amount of aluminum chloride present. We are investigating the reason for this unusual and interesting selectivity shown in the acylation of 1-benzenesulfonylpyrrole.[8]

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References

1. Funded by the Government of the Peoples Republic of China.
2. H.J. Anderson, Canad. J. Chem., 35, 21, (1957).
3. H.J. Anderson and S.J. Griffiths, Canad. J. Chem., 45, 2227, (1967).
4. 1-Benzenesulfonylpyrrole has been prepared by the reaction of pyrrolylpotassium and benzenesulfonyl chloride (E.P. Papadopoulos and N.F. Haidar, Tetrahedron Letters, 1721, (1968)). We have found that this compound can more conveniently be prepared by the phase-transfer reaction (V. O. Illi, Synthesis, 136, (1979)) in which a solution of pyrrole in dichloromethane reacts with benzenesulfonyl chloride and sodium hydroxide in the presence of the phase-transfer catalyst tetrabutylammonium hydrogen sulfate to give 1-benzenesulfonylpyrrole in 71% yield.
5. H.J. Anderson, C.E. Loader, and A. Foster, Canad. J. Chem., 58, 2527, (1980) and references contained therein.
6. All compounds showed analytical and spectral data consistent with their assigned structures. Physical and spectral data for some key compounds follows: 3-Benzoyl-1-benzenesulfonylpyrrole, mp 59-60°c; ir (Nujol mull) v: 1664 (C=O); nmr ($CDCl_3$) δ: 6.75 (1H, m), 7.17 (1H, m), 7.47-7.82 (11H, m); m/e 311. 3-Acetyl-1-benzenesulfonylpyrrole, mp 100-101°C, ir (Nujol mull) 1650 cm^{-1}; nmr δ: 2.40 (3H, s), 6.63 (1H, q), 7.07 (1H, q), 7.4-8.0 (6H, m). 3-(2-methylbenzoyl)-pyrrole, mp 94-97°C, ir ($CHCl_3$) 1635 cm^{-1} nmr ($CDCl_3$) δ: 2.39 (3H, s), 6.60 (2H, m), 6.93 (1H, m), 7.16 (4H, m), 9.43 (1H, broad). 1-Benzenesulfonylpyrrole-2-carbonitrile, mp 94.5-95°C; ir (Nujol mull) 2226 cm^{-1}; nmr ($CDCl_3$) δ: 6.27 (1H, q), 6.90 (1H, q), 7.46 (1H, q), 7.41-8.16 (5H, m). 3-(4-Methylbenzoyl)-pyrrole, mp 128-129°C, ir ($CHCl_3$) 1634 cm^{-1}; nmr ($CDCl_3$) δ: 2.39 (3H, s), 6.79 (2H, m), 7.30 (3H, m), 7.75 (2H, m), 9.90 (1H, broad). 3-(4-Methoxybenzoyl)-pyrrole, mp 105-106.5°C; ir (Nujol mull) 1605 cm^{-1}; nmr ($CDCl_3$) δ: 3.80 (3H, s), 6.70 (2H, m), 6.84 (2H, m), 7.24 (1H, m), 7.77 (2H, m), 9.73 (1H, broad).
7. K.J. Morgan and D.P. Morrey, Tetrahedron, 27, 245, (1971).
8. When this work was almost complete we learned of similar studies currently being carried out by Dr. J. Rokach and his colleagues at the Merck-Frosst Research Laboratories, Pointe-Claire, Quebec, Canada.

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